

**Double-blind controlled assessment of the effect of intra-articular hydrocortisone and urokinase in rheumatoid arthritis**

Roger D. Sturrock, M.B., M.R.C.P.,  
Caroline Watkins,  
Peter Lee, M.B., M.R.A.C.P.,  
Peter M. Brooks, M.B., M.R.A.C.P.,  
and  
W. Carson Dick, M.D., M.R.C.P.

*The Centre for Rheumatic Diseases  
and the University Department of  
Medicine, Glasgow Royal Infirmary,  
Scotland*

Curr. med. Res. Opin., (1974), 2, 288.

Received: 6th April 1974

**Summary**

*The merits of intra-articular urokinase in the treatment of rheumatoid arthritis are discussed. The results of a double-blind controlled study of its use in the knee joint following intra-articular hydrocortisone are presented.*

*Key words: Arthritis, rheumatoid – urokinase – hydrocortisone*

**Introduction**

Urokinase has been suggested to be a useful agent in the treatment of rheumatoid arthritis.<sup>5,6</sup> Altered metabolism of fibrinogen and fibrinolysis has been demonstrated in the rheumatoid joint<sup>1-3</sup> and, therefore, there may be some basis for the use of a fibrinolytic agent such as urokinase in the treatment of rheumatoid joint disease. A preliminary double-blind comparison of the effects of water and urokinase intra-articular injections on rheumatoid knees did not demonstrate a significant difference between the two forms of treatment<sup>9</sup>; however, in view of the reports that a combination of urokinase and steroid may be more effective<sup>6</sup> we proceeded to evaluate this claim further.

**Patients and methods**

Seventeen patients with classical rheumatoid arthritis (American Rheumatism Association Criteria)<sup>8</sup> who had bilateral involvement of the knee joints were included in the study. There were 10 females and 7 males, with a mean duration of arthritis of 10.5 years (range 1 to 37) and a mean age of 57.6 years (range 44 to 69). All patients were taking non-steroidal anti-inflammatory agents and 2 also received low-dose steroids throughout the duration of the trial.

Each knee joint was assessed in a standard way by one observer whose intra- and inter-observer errors for the methods used had been quantitated. The indices used to quantitate changes included knee range of movement as measured by a goniometer, the number of full flexions possible in 30 seconds, local knee pain score and <sup>99m</sup>Tc uptake. Urokinase (5000 units) was injected into one knee and 2 ml. sterile

water into the opposite knee, the order of treatment being randomised. Twenty-four hours later, 50 mg. hydrocortisone succinate was injected into each knee following aspiration with a size 19G needle and the knees assessed at weekly intervals for a period of 4 weeks.

## Results

Table I shows that there is no statistically significant difference between the water and urokinase-treated knees at the end of 4 weeks. However, within each treatment group the effect of hydrocortisone produced a significant improvement in range of movement at 1 week ( $t = 1.88$   $p < 0.05$ ) and number of full flexions in 30 seconds at 4 weeks ( $t = 5.51$   $p < 0.001$ ).

Table I. Clinical and isotopic data before and after urokinase and hydrocortisone, and hydrocortisone and water. Results expressed as mean ( $\pm$ SEM)

Measurement	Pre-urokinase +hydrocortisone	Post-urokinase +hydrocortisone			Pre-water +hydrocortisone			Post-water +hydrocortisone	
		1 week	2 weeks	4 weeks*	1 week	2 weeks	4 weeks*	1 week	4 weeks*
Pain score	1.29 ( $\pm 0.25$ )	1.11 ( $\pm 0.21$ )	0.8 ( $\pm 0.17$ )	0.84 ( $\pm 0.22$ )	1.35 ( $\pm 0.19$ )	0.61 ( $\pm 0.14$ )	0.6 ( $\pm 0.21$ )	1.15 ( $\pm 0.3$ )	
Range of movement	118.5 ( $\pm 1.16$ )	123.23 ( $\pm 3.45$ )	122.1 ( $\pm 2.99$ )	123.6 ( $\pm 3.82$ )	115.5 ( $\pm 2.93$ )	121.4 ( $\pm 3.9$ )	118.9 ( $\pm 3.19$ )	124.5 ( $\pm 2.17$ )	
No. full flexions in 30 sec.	17.2 ( $\pm 1.75$ )	19.61 ( $\pm 1.77$ )	23.94 ( $\pm 2.07$ )	22.25 ( $\pm 2.28$ )	16.94 ( $\pm 1.86$ )	20.29 ( $\pm 1.97$ )	22.88 ( $\pm 1.97$ )	22.18 ( $\pm 2.56$ )	
99mTc uptake	30.21 ( $\pm 1.60$ )		28.41 ( $\pm 2.84$ )	27.8 ( $\pm 1.48$ )	30.04 ( $\pm 1.72$ )		29.03 ( $\pm 2.46$ )	31.58 ( $\pm 1.64$ )	

\*Difference not significant

## Discussion

The results obtained must not be extrapolated beyond the time limits of the study and the patient group will be followed up carefully over a long period of time so that any further changes can be detected and reported. The assessment methods used were sufficiently sensitive to detect changes produced by intra-articular hydrocortisone, but did not demonstrate any additive effect from urokinase. Popert<sup>7</sup> has suggested that the use of a very large bore needle will allow a more adequate aspiration of fibrin debris from a joint and that this is facilitated by a prior intra-articular injection of urokinase. The needle used in our series was of the size (19G) normally employed for joint aspirations and the volume of synovial fluid and fibrin debris aspirated did not seem to be influenced by an earlier injection of urokinase.

Urokinase may well have a place in the treatment of fibrinous deposits secondary to vitreous haemorrhage in the confined space of the eye<sup>4</sup> but its use in larger cavities such as the knee joint would seem to be limited.

#### Acknowledgements

We wish to thank the Arthritis and Rheumatism Council for continued support and Mr Clyde of Leo Laboratories Ltd. for the supply of urokinase.

#### References

1. Bach, Anderson R, and Gormen, J., (1970). Fibrinolytic and fibrin stabilizing activity of synovial membrane. *Ann. rheum. Dis.*, 29, 287.
2. Barnhart, M. I., Riddle, J. M., Bluhm, G. B., and Quintana, C., (1967). Fibrin promotion and lysis in arthritic joints. *Ann. rheum. Dis.*, 26, 206.
3. Caughey, D. E., and Highton, T. C., (1967). Components of the fibrinolytic system in synovial joints. *Ann. rheum. Dis.*, 26, 297.
4. Forrester, J., (1974). Unpublished observations.
5. Ito, T., and Naito, K., (1970). Experiences with intra-articular use of urokinase. *Clin. Postgrad.*, 8, 10.
6. Morotomi, T., and Tatezawa, Y., (1970). The treatment of rheumatoid arthritis with urokinase. *Clin. Postgrad.*, 8, 8.
7. Popert, A. J., (1974). Unpublished observations.
8. Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R., and Jessar, R. A., (1959). Diagnostic criteria for rheumatoid arthritis: 1958 revision. *Ann. rheum. Dis.*, 18, 49.
9. Sturrock, R. D., Watkins, Caroline, Williamson, T., and Dick, W. C., (1974). An evaluation of the effect of intra-articular urokinase in rheumatoid arthritis. *Ann. rheum. Dis.* In press.